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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/827,688	04/06/2001	Frank M. Orson	P01949US1	5045

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EXAMINER
NGUYEN, QUANG

ART UNIT	PAPER NUMBER
1636	13

DATE MAILED: 08/11/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/827,688	ORSON ET AL.	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 July 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6-15,17-22 and 28-42* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7-15,17-21 and 28-42* is/are rejected.

7)☒ Claim(s) *6 and 22* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☒ Interview Summary (PTO-413) Paper No(s). *10* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7/09/03 has been entered.

Amended claims 1-4, 6-15, 17-22, 28-42 are pending in the present application.

Applicants previously elected without traverse genes associated with an infectious disease with HIV as a pathogenic viral genome, gastrointestinal mucosal surface and subcutaneous administration as the elected species in Paper No.5.

Response to Amendment

The rejection under 35 U.S.C. 112, first paragraph, is withdrawn in light of Applicants' amendment.

The art rejections in the previous Office Action are withdrawn in light of Applicants' amendment.

Following is a new ground of rejection necessitated by Applicants' amendment.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 41 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 41 recites the limitation "different promoter polynucleotide sequences" in line 2 of the claim. There is insufficient antecedent basis for this limitation in the claim. This is because in claim 39 from which claim 41 is dependent upon, only a first promoter polynucleotide sequence is recited, not multiple promoter polynucleotide sequences. Clarification is requested because the metes and bounds of the claim are not clearly established.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Amended claims 1, 7-8, 12, 20-21 and 42 are rejected under 35 U.S.C. 102(b) as being anticipated by Orgis et al. (Gene therapy 5:1425-1433, 1998; IDS).

Ogris et al. disclose the preparation of plasmid DNA complexes with transferrin-polyethylenimine (PEI) conjugates for transfection of cultured neuroblastoma Neuro 2A

cells, melanoma B16F10 cells, and erythroid leukemic K562 cells under physiological salt concentration or at low ionic strength (see abstract and Materials and methods section). Under physiological salt concentration, the plasmid DNA complexes with transferring-PEI conjugates form **large aggregates** (up to >1000 nm; see abstract and Figs. 1 & 3). It is further noted that during the synthesis of transferrin-PEI conjugates, transferrin molecules would be linked together in addition to them being linked to PEI molecules (see the synthesis of transferrin-PEI conjugate in the referred Kircheis et al. reference; Gene therapy 4:409-418, 1997). As transferrin molecules are proteins and they are bound together via the modification, they are also qualified as an aggregate according to the definition in the instant specification on page 8, second last paragraph. The utilized plasmid pCMVL codes for the *Photinus pyralis* luciferase gene under the control of the cytomegalovirus enhancer/promoter. The luciferase gene product is capable of provoking an immune response in certain hosts, and thereby it is an antigen. Ogris et al. teach that large plasmid DNA complexes with transferrin-polyethylenimine (PEI) conjugates formed in physiological salt conditions showed high transfection efficiency, and this finding is useful for a series of *in vitro* transfections and also **localized *in vivo* applications** (page 1431, col. 2, top of last paragraph). However, Ogris et al. note that small particles should be preferred for a series of *in vivo* applications, such as intravenous administration.

Accordingly, the instant claims read over the teachings of Ogris et al., and therefore the reference anticipates the instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Amended claims 1-4, 7-15, 17-21 and 28-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Johnston et al. (U.S. Patent No. 5,703,057) in view of Orgis et al. (Gene therapy 5:1425-1433, 1998; IDS).

Johnston et al. disclose a composition comprising expression vectors encoding antigens prepared from gene sequences derived from a pathogenic virus, including HIV, for expression in a mammalian cell and a method for generating an immune response into a mammal using the same via various modes of administration including parenteral as well as mucosal routes (see Summary of Invention, cols. 2-8; col. 11). Johnston et al. further teach that mammalian genes fused to the pathogen DNA can facilitate

expression in the mammalian cell, specifically human growth hormone, ubiquitin, signal sequences and others (col. 5, lines 19-29). Johnston et al. disclose that fusion of non-mammalian pathogen sequences to mammalian genes increases the amount of antigen available to the immune system due to increasing antigenic recognition or targeting to components in the cell.

Johnston et al. do not teach that the expression vectors encoding antigens prepared from gene sequences derived from a pathogenic virus, including HIV, for expression in a mammalian cell are bound to an aggregated protein-polycationic polymer conjugates.

However, at the effective filing date of the present application Ogris et al. already disclose the preparation of plasmid DNA complexes with transferrin-polyethylenimine (PEI) conjugates for transfection of cultured neuroblastoma Neuro 2A cells, melanoma B16F10 cells, and erythroid leukemic K562 cells under physiological salt concentration or at low ionic strength (see abstract and Materials and methods section). Under physiological salt concentration, the plasmid DNA complexes with transferring-PEI conjugates form **large aggregates** (up to >1000 nm; see abstract and Figs. 1 & 3). It is further noted that during the synthesis of transferrin-PEI conjugates, transferrin molecules would be linked together in addition to them being linked to PEI molecules (see the synthesis of transferrin-PEI conjugate in the referred Kircheis et al. reference; Gene therapy 4:409-418, 1997). As transferrin molecules are proteins and they are bound together via the modification, they are also qualified as an aggregate according to the definition in the instant specification on page 8, second last paragraph. Most

importantly, Ogris et al. teach that large plasmid DNA complexes with transferrin-polyethylenimine (PEI) conjugates formed in physiological salt conditions showed **high transfection efficiency**, and this finding is useful for a series of *in vitro* transfections and also **localized *in vivo* applications** (page 1431, col. 2, top of last paragraph).

Accordingly, at the time of the instant invention it would have been obvious and within the scope of skill for an ordinary skilled artisan to modify the method of Johnston et al. by preparing and utilizing the composition comprising expression vectors encoding antigens prepared from gene sequences derived from a pathogenic virus, including HIV, bound to a ligand-PEI conjugate for antigen expression in a mammalian cell at a target tissue or site to enhance the amount of antigen available to the host immune system via increased transfection efficiency of plasmid vector/transferrin-polyethylenimine (PEI) conjugate aggregates formed under physiological salt concentrations according to the teachings of Orgris et al.

An ordinary skilled artisan would have been motivated to make this modification because as taught by Ogris et al., plasmid vector/transferrin-polyethylenimine (PEI) conjugate aggregates formed under physiological salt concentrations have a high transfection efficiency to cells. An enhanced cell transfection rate would be advantageous for induction of a host immune response specific to an antigen due to an increased in the amount of antigen available to the host immune system.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Amended claims 32-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Johnston et al. (U.S. Patent No. 5,703,057) in view of Orgis et al. (Gene therapy 5:1425-1433, 1998; IDS) and Weiner et al. (U.S. 6,348,449).

The teachings of Johnston et al. and Ogris et al. have been discussed above. However, none of the references teaches a method for inducing an immune response in a mammal by co-administering into the mammal two expression vectors, both bound to an aggregated protein-polycationic polymer conjugate wherein the first expression vector comprises a promoter polynucleotide sequence operatively linked to a polynucleotide sequence encoding an antigen and the second vector comprises a cytokine polynucleotide sequence, or the a method of inducing an immune response in a mammal by administering an expression vector coding an antigen and a cytokine bound to an aggregated protein-polycationic polymer conjugate.

However, at the effective filing date of the present application, Weiner et al. already teach that for immunization applications, the genetic construct contains nucleotide sequences that encode a target protein and further include genes for proteins which enhance the immune response against such target protein. Examples of such genes are those encoding cytokines and lymphokines such as GM-CSF, IL-2, PDGF, IL-1, and others (line 60 of col. 5 continues to line 4 of col. 6, and see the claims).

Accordingly, at the time of the instant invention it would have been obvious and within the scope of skill for an ordinary skilled artisan to further modify the method of Johnston et al. and Ogris et al. by further incorporating a cytokine expression vector

bound to the same aggregated protein-polycationic polymer conjugate or using an expression vector encoding both an antigen and a cytokine that is bound in an aggregated protein-polycationic polymer conjugate to enhance the immune response against target protein, for this instance antigens prepared from gene sequences derived from a pathogenic virus, such as HIV, based on the teachings of Weiner et al. It would also have been obvious and within the scope of skill for an ordinary skilled artisan to use the same or different promoters for expressing the sequences encoding an antigen and a cytokine as long as the antigen and cytokine are expressed.

An ordinary skilled artisan would have been motivated to make the above modification because as taught by Weiner et al., the co-expression of cytokines and lymphokines such as GM-CSF, IL-2 and others can enhance an immune response against the desired target protein.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Conclusions

Claims 6 and 22 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (703) 308-8339.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, David Guzo, Ph.D., may be reached at (703) 308-1906, or SPE, Remy Yucel, Ph.D., at (703) 305-1998.

Quang Nguyen, Ph.D.

DAVID GUZO
PRIMARY EXAMINER